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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
06267.0165-00000

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Application Number	Filed
10/510,020	April 28, 2005

First Named Inventor
Jukka SALLINEN

Art Unit	Examiner
1628	Kathrien Ann CRUZ

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.

■ attorney or agent of record.
Registration number 63,219.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

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October 19, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Applicants request a pre-appeal brief panel review of the rejections set forth in the Final Office Action dated May 24, 2010 ("Final Office Action"). This request is being filed concurrently with a Notice of Appeal under 37 C.F.R. § 41.31, the appropriate fee, and a completed form PTO/SB/33. No amendments are being filed with this Request.

The Office rejected claims 1, 2, 7, 9, 10, 13-15, 17, and 18 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent Nos. 5,902,807 ("Haapalinna") and 5,492,907 ("Pickar") in view of Parwani, A. et al., "Impaired Prepulse Inhibition of Acoustic Startle in Schizophrenia," *Biol. Psych.* (2000) 47:662-669 ("Parwani"). Final Office Action at 2.

The Office contends that Haapalinna "clearly teaches that alpha-2-adrenoreceptor antagonist useful for the treatment of a mental illness said antagonist being selective for the alpha-2C-adrenoreceptor subtype," and Pickar "clearly teaches a method for treating schizophrenia and schizoaffective illnesses . . . [a]nd since Parwani teaches that schizophrenia patients are known for having reduced sensorimotor gating . . . [i]t would have been obvious to one of ordinary skill[] in the art to treat sensorimotor gating deficits with an alpha-2C-adrenoreceptor." Final Office Action at 3 (emphasis omitted). Applicants respectfully disagree with this rejection for at least the reasons that one of ordinary skill in the art would not have been led to combine Haapalinna and Pickar and that there would have been no reasonable expectation of success in making the proposed combination. *See* M.P.E.P. § 2143.

In an obviousness determination, the Office must consider the reference teachings as a whole, taking into consideration portions where the references teach away from their combination, as in the present case. M.P.E.P. § 2145(X)(D)(2); *see also In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (holding that the combination of references was improper where one taught the interchangeability of antimony and an alkali metal and the other expressly excluded antimony). The conflicting teachings of Haapalinna and Pickar would not have led one of ordinary skill in the art to combine their teachings but, rather, would have led them away from making such a combination. As a result, the Office has failed to establish a *prima facie* case of obviousness.

Haapalinna teaches that there are three subtypes of alpha-2-adrenoceptors in humans and discloses methods for treating stress-induced mental disorders, such as

anxiety and post-traumatic stress disorder, with antagonists that are ***selective*** for the alpha-2C-adrenoceptors subtype. Haapalinna at col. 2, ll. 34-44. Indeed, Haapalinna particularly states that "the antagonist should have . . . a ten-fold preference to the alpha-2C subtype over the other alpha-2-subtypes." Haapalinna at col. 3, ll. 8-9.

Haapalina hypothesizes that "a behavioral response of a subtype C selective alpha-2-adrenoceptor antagonist would be different from that of a non-subtype selective." Haapalinna at col. 1, ll. 33-36. And Haapalina proved their hypothesis, finding that the non-selective antagonists—in contrast to the alpha-2C selective antagonists—1) did **not** prevent the propagation of stress-induced behavioral despair (col. 6, ll. 1-6); 2) "did **not** provide any anxiolytic [i.e., anxiety reducing] response" (col. 7, ll. 14-19 (emphasis added)); and 3) **potentiated** neophobic stress (col. 7, ll. 44-49). Moreover, Haapalinna states that non-specific alpha-2-adrenoceptor antagonists actually **cause anxiety**, one of the very conditions that Haapalinna seeks to treat. Haapalinna at col. 1, ll. 18-19 ("Conventionally antagonists of alpha-2-adrenoceptors, such as yohimbine, have been found to be anxiogenic [i.e., anxiety producing].")

In contrast, Pickar discloses methods of treatment for schizophrenia and other psychotic illnesses using ***non-selective*** alpha-adrenoceptor antagonists in combination with D_2 dopamine receptor antagonists - the very type of antagonist taught away from in Haapalinna. Pickar at col. 2, ll. 64-67. For example, Pickar discloses that idazoxan, a non-specific alpha-2-adrenoceptor antagonist, is a particularly preferred embodiment (col. 2, ll. 64-67) and it is, in fact, the only alpha-2 adrenoceptor antagonist used in Pickar's examples (Examples 1 and 2). Yet, idazoxan is one of the listed examples of non-selective type of alpha-2-adreoceptor antagonist in Haapalinna and from which Haapalinna teaches away. Haapalinna at col. 1, ll. 25-28.

Therefore, in view of the contradictory nature of the teachings in Haapalinna and Pickar, nothing would have led one of ordinary skill in the art to combine those teachings. Rather, in view of Haapalinna's unfavorable comparison of non-selective antagonists, like those disclosed in Pickar, to selective alpha-2C-adrenoceptor antagonists, one of ordinary skill in the art would not even have looked to Pickar in the first place. Furthermore, Haapalinna's clear preference for selective alpha-2C-adrenoceptor antagonists undermines any reasonable expectation of success one of

ordinary skill in the art might have had in substituting non-selective alpha-C-adrenoceptor antagonists into Haapalinna's methods. Accordingly, the Office has failed to establish a *prima facie* case of obviousness.

Furthermore, Applicants demonstrated in the as-filed specification that an exemplary alpha-2C-adrenoceptor antagonist is significantly better than a non-selective antagonist. As discussed in Parwani, sensorimotor gating deficiencies can be observed by a decreased prepulse inhibition (PPI) attributed to sensory flooding and cognitive fragmentation. Parwani at 662. In other words, patients with sensorimotor gating defects are unable to shut out trivial sensory stimulation and are surprised by a startling event even when a pre-pulse, a.k.a. warning, is given. Applicants' presently claimed inventions increase this PPI inhibition, e.g., help to eliminate sensory flooding, using alpha-2C-adrenoceptor antagonists. One such exemplary alpha-2C antagonist was shown to dose dependently and significantly increase PPI. Specification at page 5, ll. 3-7, page 3, ll. 19-27, and Figure 2B. In stark contrast, a non-selective alpha-2 antagonist not only increased the startle reflex *per se*, it also showed no effect on PPI in the mouse model. Specification, page 5 ll. 7-11, page 3, ll. 19-27, and Figures 2A and 2B. Thus, both Haapalinna and the teachings in the as-filed application clearly demonstrate distinct and differing effects resulting from the use of selective and non-selective alpha-2-adrenoceptor antagonists.

Moreover, contrary to the Office's assertion on page 5 of the Office Action, Haapalinna does **not** disclose that alpha-2C antagonists treat mental illness broadly. As previously noted, Haapalinna discloses that alpha-2C adrenoceptor antagonists are useful to treat **stress-induced** mental illnesses, not all mental illnesses in general. As such, one of ordinary skill in the art would not have been led to combine Haapalinna and Pickar for the additional reason that mental illnesses are not all the same. Indeed, different mental illnesses can have very different etiologies and mechanisms of action. And one of ordinary skill in the art would have known that the non-selective alpha-2-adrenoceptor antagonists of Pickar would not necessarily affect the sensorimotor gating defects in schizophrenic patients, because schizophrenia and the other psychotic illnesses disclosed in Pickar result from many interconnected physiochemical imbalances, not only from sensorimotor gating defects. Indeed, Applicants' own

specification shows that the non-specific antagonists of Pickar likely would not affect the sensorimotor gating deficiencies because atipamezole, a non-specific alpha-2-adrenoceptor antagonist, not only significantly increased the startle reactivity in the mouse model, it also had no effect on the PPI phenomenon. Specification, page 5, ll. 3-11, and Figures 2A and 2B.

Therefore, for the additional reason that not all mental illnesses are equal or treated by the same medicaments, one of ordinary skill in the art would not have been led to combine the teachings from Haapalinna, that discusses stress-induced illnesses such as anxiety, with the teachings of Pickar, which discusses psychotic illnesses such as schizophrenia. No reasonable expectation of success existed that a possible effect of treating sensorimotor gating defects in schizophrenic patients is necessarily an effect when treating stress-induced illnesses.

Although the Office relies on Parwani for the teaching "that schizophrenic patients are known for having reduced sensorimotor gating," Applicants respectfully submit that the primary references hardly provide a starting point for an obviousness rejection. In addition, Parwani fails to compensate for the conflicting teachings of Haapalinna and Pickar, as Parwani solely focuses on characterizing PPI and habituation deficits in schizophrenic patients. Parwani at Abstract.

For the reasons of record and the reasons presented above, the Office has not established a *prima facie* case of obviousness. As a result, this rejection should be withdrawn.

The Office rejected claim 16 under 35 U.S.C. § 103(a) as being unpatentable over Haapalinna, Pickar, and Parwani, and further in view of U.S. Patent No. 6,593,324 ("Wurster"). Final Office Action at 9. Applicants respectfully disagree with and traverse this rejection. Haapalinna, Pickar, and Parwani are discussed above. The Office admits that "[n]one of cited references expressly teach[es] acridin-9-yl-[4-(4-methylpiperazin-1-yl)-phenylamine." *Id.*

The Office concludes that

> [i]t would have been obvious to one of ordinary skills in the art to employ acridin-9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine for the treatment of schizophrenia and sensorimotor gating deficits as taught by Parwani and Wurster. One would have been motivated to employ acridin-

> 9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine for the treatment of schizophrenia and sensorimotor gating deficits because it is known in the art that alpha-2 adrenoceptors are effective in the treatment of schizophrenia and sensorimotor gating deficits often associated with schizophrenia as taught by Wurster.

Id. at 9-10. Although Wurster discloses that its compounds, including acridin-9-yl-[4-(4-methylpiperazin-1- yl)-phenylamine, may be used to treat schizophrenia (col. 24, ll. 30 and 39-40), Wurster fails to compensate for the deficiencies of Haapalinna, Pickar, and Parwani, as discussed above. Even though Wurster discloses that an alpha-2C-adrenoceptor antagonist may be used to treat schizophrenia, it—like the other cited art—is wholly silent with respect to whether alpha-2C antagonists may be able to ameliorate sensorimotor gating deficits, such as recited by the present claims. And, one of ordinary skill in the art would not have been able to infer such activity because Wurster discloses that its compounds can be used to treat many different conditions (col. 24, ll. 32-53), some of which are not even CNS disorders, let alone tied to sensorimotor gating defects. Thus, a skilled artisan would not have been motivated to use the compounds of Wurster "for [treating] at least one symptom of a disorder or condition associated with sensorimotor gating deficits."

That sensorimotor gating defects were known to be present in schizophrenic patients (Parwani) has no bearing on the fact that it was not known, at the time of invention, that alpha-2C antagonists had beneficial action on sensorimotor gating deficits. As a result, a *prima facie* case of obviousness has not been established because "obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." M.P.E.P. § 2141.02(V) (citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d (BNA) 1955, 1957 (Fed. Cir. 1993)). For at least this reason, this rejection should be withdrawn.

In view of the foregoing remarks, Applicants respectfully request reconsideration of the current rejections and timely allowance of all pending claims. Please grant any extensions of time required to enter this paper and charge any additional required fees to Deposit Account No. 06-0916.